

What is claimed is:

1. A method of fabricating a biopolymer array from biomonomers comprising the steps of:
 - 5 (a) depositing a biomonomer in solution onto a substrate for linking to a surface of the substrate in an array pattern of features;
 - (b) deprotecting the linked biomonomer, such that the linked biomonomer can react with subsequent biomonomers in solution;
 - (c) depositing a subsequent biomonomer and an activation reagent in solution onto the features, the subsequent biomonomer being activated for attachment to the linked biomonomer on the array feature by the activation reagent, the subsequent biomonomer becoming the linked biomonomer upon attachment;
 - 10 (d) applying a non-miscible fluid (NMF) over the feature locations on the surface of the substrate before or after any of the above steps (a) to (c), the NMF being inert and insoluble with the biomonomer solution, the activation reagent, the activated biomonomer and the linked biomonomer; and
 - 15 (e) repeating at least step (c) until the biopolymer is synthesized at each feature.
2. The method of Claim 1, wherein the biopolymer array comprises multiple different array features and steps (a) through (d) are repeated at each of multiple different features on the same substrate, to produce the array of multiple different biopolymers.
3. The method of Claim 1, wherein the step of applying (d) the NMF comprises the step of depositing an amount of NMF so as to cover an area greater than the area of each feature.
4. The method of Claim 3, wherein the step of depositing an amount of NMF comprises the step of depositing a droplet of NMF on each feature that is large enough to completely cover the feature, and wherein the steps (a) and (c) of depositing the biomonomers comprise the steps of:

loading the biomonomer in solution into a pulsejet of a deposition system; positioning the pulsejet over the NMF droplet on the surface of the array; ejecting the biomonomer from the pulsejet into the NMF droplet and to the feature;

- 5 moving the pulse jet to a next feature; and
repeating the steps of positioning, ejecting and moving for each applicable feature location until the biomonomer is deposited on all applicable features.

- 10 5. The method of Claim 3, wherein the step of depositing an amount of NMF comprises the step of covering the entire array surface and completely covering the features with the NMF.

6. The method of Claim 5, wherein the steps (a) and (c) of depositing the biomonomers comprise the steps of:

- 15 15 loading the biomonomer in solution into a pulsejet of a deposition system; immersing the pulsejet into the NMF over a feature on the surface of the array; ejecting the biomonomer from the pulsejet to the feature; moving the immersed pulse jet to a next applicable feature location and ejecting the biomonomer to the applicable feature; and
20 20 repeating the step of moving and ejecting until the biomonomer is deposited on all applicable features.

7. The method of Claim 5, wherein the steps (a) and (c) of depositing the biomonomers comprise the steps of:

- 25 25 loading the biomonomer in solution into a pulsejet of a deposition system; immersing the pulsejet into the NMF over a feature on the surface of the array; ejecting the biomonomer from the pulsejet to the feature; removing the pulse jet from the NMF and moving the pulse jet to a next applicable feature location; and
30 30 repeating the steps of immersing, ejecting and removing over each applicable synthesis site until the biomonomer is deposited on all applicable features.

8. The method of Claim 5, wherein the steps (a) and (c) of depositing the biomonomers comprise the steps of:

5 loading the biomonomer in solution into a pulsejet of a deposition system;
positioning the pulsejet above the NMF over a feature location on the surface of
the array;
ejecting the biomonomer from the pulsejet and into the NMF to the feature;
moving the pulse jet to a next applicable feature location; and
repeating the steps of positioning, ejecting and moving over each applicable
10 feature location until the biomonomer is deposited on all applicable features.

9. The method of Claim 5, wherein the steps (a) and (c) of depositing the biomonomers comprise the steps of:

15 loading the biomonomer in solution into a pulsejet of a deposition system;
immersing the array surface into the NMF and aligning a feature on the array
surface with the pulsejet;
ejecting the biomonomer from the pulsejet to the feature;
moving the array such that a next applicable feature location is aligned with the
pulse jet; and
20 repeating the steps of ejecting and moving for each applicable feature location
until the biomonomer is deposited on all applicable features.

10. The method of Claim 1, wherein the NMF has a density that is
different from the density of the biomonomer solution.

25 11. The method of Claim 10, wherein the NMF has a lower density than
the density of the biomonomer solution.

30 12. The method of Claim 10, wherein the NMF has a higher density than
the density of the biomonomer solution.

13. The method of Claim 1 further comprising the steps of:
(d') deactivating unreacted activation reagent, the deactivation reagent having a density that is different from the NMF; and
5 (d'') removing the NMF, reagents, and unreacted biomonomer solution from the array surface before the step (e).

14. The method of Claim 13, wherein the step of deactivating (d') comprises hydrolyzing the activation reagent and unreacted biomonomer.

10 15. The method of Claim 13, wherein the biopolymer is an oligonucleotide or polynucleotide; the biomonomers are selected from phosphoramidites, phosphites or H-phosphonates; the solution comprises a solvent selected from acetonitrile, propylene carbonate or adiponitrile; the activation reagent is selected from tetrazole, 15 ethylthiotetrazole, dicyanoimidazole or benzimidazolium triflate; the deactivation reagent is selected from methanol, water, an alkyl alcohol, a halogenalkylalcohol, or trichloroethanol; and wherein the NMF is selected from heptane, octane, nonane, decane, undecane, dodecane, tridecane, tetradecane, pentadecane, hexadecane, heptadecane, cycloheptane, cyclooctane, cyclononane, and cyclodecane.

20 16. The method of Claim 1, where the NMF is applied after the biomonomer is linked to the surface of the substrate, but before the subsequent biomonomer and activation reagent are deposited.

25 17. The method of Claim 1, where the NMF is applied before the biomonomer is deposited and linked to the surface of the substrate.

30 18. A method of fabricating a biopolymer array from biomonomers, wherein a biopolymer is synthesized on the array by depositing and linking a biomonomer solution to a feature location on a surface of an array, deprotecting the linked biomonomer to couple to subsequent biomonomer solution, and depositing a

subsequent biomonomer and an activation reagent onto the feature location to couple with the linked biomonomer, wherein the above steps are repeated to form a different biopolymer sequence at multiple feature locations on the array, the method comprising the step of:

5 applying a non-miscible fluid (NMF) over the feature locations on the surface of the array, the NMF being inert and insoluble with the biomonomer solution and activation reagent.

10 19. The method of Claim 18, where the NMF is applied after the biomonomer is linked to the surface of the array, but before the subsequent biomonomer and activation reagent are deposited.

20. The method of Claim 18, where the NMF is applied before the biomonomer is deposited and linked to the surface of the array.

15 21. The method of Claim 18, wherein the step of applying a NMF comprises the step of depositing an amount of NMF so as to cover an area greater than the area of each feature location.

20 22. The method of Claim 21, wherein the step of depositing an amount of NMF comprises the step of covering the entire array surface and feature locations with the NMF.

25 23. The method of Claim 18, wherein the NMF has a density that is different from the density of the biomonomer solution.

24. The method of Claim 23, wherein the NMF has a lower density than the density of the biomonomer solution.

30 25. The method of Claim 23, wherein the NMF has a higher density than the density of the biomonomer solution.

26. The method of Claim 18 further comprising the steps of:
deactivating unreacted activation reagent with a deactivation reagent, the
5 deactivation reagent having a density that is different from the NMF, the NMF being
inert and insoluble in the deactivation reagent; and
removing the NMF, reagents and unreacted biomonomer solution from the array
surface before another biomonomer is deposited onto the array.

10 27. The method of Claim 26, wherein the step of deactivating comprises
hydrolyzing the activation reagent and unreacted biomonomer.

15 28. The method of Claim 26, wherein the biopolymer is an oligonucleotide
or polynucleotide and the biomonomers are selected from phosphoramidites,
phosphites or H-phosphonates; the solution comprises a solvent selected from
acetonitrile, propylene carbonate or adiponitrile; the activation reagent selected from
tetrazole, ethylthiotetrazole, dicyanoimidazole or benzimidazolium triflate; the
deactivation reagent is selected from methanol, water, an alkyl alcohol, a
halogenalkylalcohol, or trichloroethanol; and wherein the NMF is selected from
20 heptane, octane, nonane, decane, undecane, dodecane, tridecane, tetradecane,
pentadecane, hexadecane, heptadecane, cycloheptane, cyclooctane, cyclononane, and
cyclodecane.

25 29. A method of fabricating a biopolymer array from pre-synthesized
biopolymers, wherein the array has a surface that is prepared for linking with the pre-
synthesized biopolymers, and wherein the pre-synthesized biopolymers are in solution
for linking to the prepared surface, the method comprising the steps of:
adding a non-miscible fluid (NMF) to the array surface, the NMF being inert,
immiscible and insoluble in aqueous solution; and
30 depositing the biopolymer solution on the array surface and linking the
biopolymer to the surface.

30. The method of claim 29 wherein the biopolymer solution is deposited on the array surface through the NMF.

5 31. The method of claim 29 wherein the biopolymers are deprotected and in an aqueous solution, the method additionally comprising removing the NMF and unlinked biopolymer solution from the surface.

10 32. The method of Claim 29, wherein the step of adding the NMF comprises the step of applying a quantity of NMF to completely cover the array surface; and wherein the step of depositing comprises the step of loading the biopolymer solution into a pulsejet of a deposition system and ejecting the solution as droplets through the NMF to the array surface for linkage.

15 33. The method of claim 32 wherein the biopolymer in the loaded solution is deprotected.

20 34. The method of Claim 29, wherein the step of adding the NMF comprises the step of applying a quantity of NMF sufficient to cover each one of a plurality of feature locations where the biopolymer will be linked on the array surface; and wherein the step of depositing comprises the step of loading a deprotected biopolymer solution into a pulsejet of a deposition system and ejecting the solution as droplets into the NMF at the feature location for linkage.

25 35. The method of Claim 29, wherein the step of adding the NMF comprises the step of immersing the prepared array surface into a quantity of NMF; and wherein the step of depositing comprises the step of loading a deprotected biopolymer solution into a pulsejet of a deposition system and ejecting the solution as droplets through the NMF to the array surface for linkage.

36. A method of shielding biosynthesis reactions and sensitive biosynthesis reactants from the ambient environment comprising the steps of:

- (a) applying a non-miscible fluid (NMF) to one or more sites where the biosynthesis reactions take place, the NMF being inert and insoluble with respect to the biosynthesis reactions and the biosynthesis reactants, the NMF covering the one or more sites; and
- (b) depositing one or more of the sensitive biosynthesis reactants through the NMF on the one or more sites.

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37. A shield which protects sensitive biosynthesis reactions and biosynthesis reactants from the ambient environment comprising:

- a non-miscible fluid (NMF) applied to cover the biosynthesis reactions, the NMF being inert and insoluble with respect to the biosynthesis reactions and the biosynthesis reactants.

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